Scientific Research Publishing

Journal of Biosciences and Medicines, 2025, 13(4), 170-179
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Exploring the Association between Inflammatory Factors and the Development of Pathological Scars

Zhuohua Liang[1], Yongxian Rong[2*]

[1]School of Clinical Medicine, Youjiang Medical College for Nationalities, Baise, China
[2]Department of Burn and Plastic Surgery, Guiping People's Hospital, Guiping, China
Email: 1838639153@qq.com, *rongyongxian138@sina.com

How to cite this paper: Liang, Z.H. and Rong, Y.X. (2025) Exploring the Association between Inflammatory Factors and the Development of Pathological Scars. *Journal of Biosciences and Medicines*, **13**, 170-179.
https://doi.org/10.4236/jbm.2025.134016

Received: March 10, 2025
Accepted: April 14, 2025
Published: April 17, 2025

Abstract

Pathological scars are a type of disease characterized by abnormal fibrous hyperplasia, including two types: hypertrophic scars and keloids. They are the result of abnormal hyperplasia during the process of skin wound healing, which seriously affects the appearance and quality of life of patients. In recent years, an increasing number of studies have shown that the inflammatory response plays a crucial role in the formation and development of pathological scars. Inflammation is a defensive response of the body to injury or infection, involving the interaction of multiple cells, mediators, and signaling pathways. During the process of skin wound healing, the inflammatory response stage is essential for clearing pathogens and promoting tissue repair. However, excessive inflammatory response or abnormal release of inflammatory mediators may lead to abnormal hyperplasia of scar tissue. Studies have found that the expression levels of various inflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and transforming growth factor-β (TGF-β), etc., are significantly higher in pathological scar tissues than in normal skin tissues. These inflammatory factors participate in the formation of pathological scars through multiple pathways, such as activating fibroblasts, inducing excessive deposition of the extracellular matrix, and promoting angiogenesis. Oxidative stress and the regulation of microRNAs can induce the expression and release of inflammatory factors, thus indirectly promoting the formation of pathological scars. Through a comprehensive analysis of relevant domestic and foreign literature, this study systematically expounds the specific mechanisms of action of inflammatory factors, fibroblasts, oxidative stress, and microRNAs in the occurrence and development of pathological scars.

Keywords

Inflammatory Factors, Fibroblasts, Oxidative Stress, MicroRNA

1. Overview of Inflammatory Factors

Wound healing constitutes a dynamic and complex biological process characterized by the precise coordination of multiple cell types. During this process, various cells exhibit distinct functions and contributions in the hemostasis phase, inflammatory response, tissue proliferation, and remodeling stages. Inflammatory factors are a class of biologically active molecules that play a crucial role in the inflammatory response, including pro-inflammatory factors and anti-inflammatory cytokines. A large number of factors, such as IL-6, IL-8, IL-18, chemokine-like factor-1 (CKLF-1), and prostaglandins produced by cyclooxygenase (COX-1), exhibit pro-inflammatory effects in tissue injury [1]. The main inflammatory factors involved in keloid formation include interleukin-6 (IL-6), transforming growth factor-β (TGF-β), and tumor necrosis factor-α (TNF-α) [2]. IL-10 and NF-κB [3] are also factors involved in scar formation. IL-6 is a lymphokine mainly produced by fibroblasts and activated T cells, which can accelerate B cell proliferation, promote cell differentiation and natural killer cell lysis, and is an important indicator for clinical infectious diseases [4]. IL-6 is a key pro-inflammatory cytokine, and the inflammatory response it mediates is a critical factor in keloid pathogenesis [5]. It induces fibroblast differentiation into myofibroblasts through the JAK/STAT3 pathway, promoting the expression of α-SMA and COL1A1 and scar formation. TGF-β is a cytokine involved in the regeneration stage of the healing process. TGF-β is present in all tissues and consists of three subtypes: β1, β2, and β3. Overexpression or imbalance of TGF-β can lead to excessive extracellular matrix deposition, thereby exacerbating scar formation. NF-κB, as a key inflammatory-related transcription factor, is widely involved in regulating gene expression and signal transduction pathways related to the inflammatory response. It has been extensively studied in the context of cellular immune responses, particularly in the pathological mechanisms of infection, inflammation, and autoimmune diseases. Reports have shown that NF-κB can upregulate the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [6]. TNF-α activates the NF-κB signaling pathway, upregulates the expression of IL-6 and IL-8, and promotes fibroblast proliferation. Macrophages are the main cells expressing the anti-inflammatory cytokine IL-10. IL-10 can inhibit the pro-inflammatory cytokines to exert anti-inflammatory effects [7]. Studies have shown that IL-10 regulates the TLR4/NF-κB pathway in dermal fibroblasts through the IL-10R/STAT3 axis, reducing ECM protein deposition and fibroblast transformation into myofibroblasts, thereby alleviating LPS-induced skin scar formation [8]. The anti-inflammatory and anti-scar effects of IL-10 have also been confirmed in gene knockout animal experiments. Pro-inflammatory factors and anti-inflammatory factors in-

teract to form a complex network that regulates the development and outcome of inflammation.

2. Role of Inflammatory Factors in the Formation of Pathological Scars

2.1. Inflammatory Response and Wound Healing

Due to various reasons, skin surface injuries occur frequently [9]. During the process of tissue damage, there is a common response to the injury, including several overlapping events, known as wound healing. Wound healing is a dynamic process involving many cellular participants and structures, and these cellular and molecular events are highly coordinated and controlled [10]. Normal wound healing is divided into three stages: the inflammatory phase, the proliferative/granulation phase, and the maturation/remodeling phase. After skin injury, inflammation first occurs in the local tissue [11]. The inflammatory process begins with tissue damage, which activates platelets, neutrophils, and macrophages, prompting them to release inflammatory mediators and cytokines, thereby participating in the recruitment of inflammatory cells, fibroblasts, endothelial cells, and epithelial cells. The subsequent proliferative stage is characterized by the activation of fibroblasts, the differentiation of myofibroblasts, and the accumulation and deposition of extracellular matrix (ECM). The third healing stage is matrix remodeling, including scar tissue remodeling [12]. In the early stage of repair, inflammatory cells exert pro-inflammatory effects through cytokines. Usually, the repair and healing stage begins after 72 hours, and collagen remodeling is ultimately completed [13]. Studies have shown that chronic inflammatory responses are associated with scar formation [14]. Inflammation is involved in the regulation of collagen synthesis. However, excessive inflammatory responses can lead to an imbalance between the synthesis and degradation of extracellular matrix, thereby forming pathological scars. The intensity of inflammation is positively correlated with the size of the final scar.

2.2. Release and Interaction of Inflammatory Factors

The inflammatory phase is the initial stage of wound healing, and the inflammatory response plays a crucial regulatory role in the outcome of wound healing. Excessive and intense inflammation leads to the infiltration of inflammatory cells into the wound site, generating a series of inflammatory cytokines, including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α). These factors, in turn, promote fibroblast proliferation and excessive collagen secretion, thereby facilitating the formation of hypertrophic scars (HSs) [15].

Approximately two hours after skin tissue damage, neutrophils are guided to the injury site by inflammatory signals released by platelets and the resident immune cell population in the tissue (including macrophages, dendritic cells, and mast cells) to respond. Resident immune cells in the tissue are mature innate immune cells that develop in the surrounding tissue and remain throughout their

lifetime [16]. Resident immune cells secrete various chemokines that promote neutrophil recruitment and chemotaxis, *i.e.* migration to the wound site. Neutrophils are among the first inflammatory cells to arrive at the injury site. They play a key role in clearing debris and preventing infection by releasing reactive oxygen species, proteases, antimicrobial peptides, and neutrophil extracellular traps (NETs), and by phagocytosing and killing pathogens [17]. Mast cell-derived mediators enhance the expression of factor XIIIa in dermal dendritic cells by releasing TNF-α, which helps with hemostasis and clot formation and stabilizes the clot. Keratinocytes recruit mast cells to the site by secreting stem cell factor (SCF). Mast cells then release a series of inflammatory mediators, including histamine, vascular endothelial growth factor (VEGF), IL-6, and IL-8, which play a crucial role in increasing endothelial cell permeability and promoting vasodilation, and effectively induce the directional migration of inflammatory cells, especially monocytes and neutrophils, to the damaged area. Mast cells can activate fibroblasts and keratinocytes, which are the main cells involved in wound healing. During the proliferation stage, mast cells promote the division and proliferation of fibroblasts through the action of IL-4, vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF), thereby generating new extracellular matrix (ECM) components. Mast cell-derived mediators, including fibroblast growth factor-2, VEGF, platelet-derived growth factor (PDGF), TGF-β, nerve growth factor (NGF), IL-4, and IL-8, contribute to angiogenesis, fibrogenesis, or re-epithelialization during the repair process [18]. The primary source of wound-associated macrophages is the circulating monocyte pool in the blood, which enters the injury site through vascular leakage, while skin-resident macrophages are a secondary source. At the injury site, resident macrophages polarize to an inflammatory phenotype, sometimes referred to as the M1 phenotype, in response to local pathogens, necrotic tissue residues, and various factors such as IFN-γ derived from natural killer cells. M1 macrophages secrete pro-inflammatory factors such as IL-1β, IL-6, IL-12, IL-23, and TNF-α, further stimulating monocyte infiltration. Secreted IL-1 increases collagen synthesis and promotes the proliferation of fibroblasts and keratinocytes [19]. Factors such as IL-1β, IL-6, IL-12, IL-23, and TNF-α not only activate immune cells but also promote the proliferation and differentiation of fibroblasts and induce the synthesis of extracellular matrix. At the same time, their complex interactions further intensify the intensity and persistence of the inflammatory response.

2.3. Growth Factors and Scar Formation

During the inflammatory phase, inflammatory cells release various growth factors that serve as core regulatory elements in tissue repair. These polypeptides, secreted by activated cells in the injured area, promote cell division and recruit new cells to the wound site. Among them, platelet-derived growth factor (PDGF) is rapidly released from damaged platelet α-granules, attracting neutrophils, macrophages, and fibroblasts while acting as a potent mitogen [20]. PDGF enhances fi-

broblast proliferation and migration via the PI3K/AKT/mTOR pathway and induces VEGF expression, synergistically promoting scar vascularization (studies show PDGF receptor inhibitors reduce scar thickness). Platelets also release TGF-β, a key cytokine with diverse roles in wound healing and fibrosis. TGF-β1 synergizes with PDGF by upregulating PDGF receptor expression, amplifying fibroblast sensitivity to PDGF. VEGF interacts with inflammatory factors: IL-6 stimulates VEGF secretion via the STAT3 pathway, forming an "inflammation-angiogenesis-fibrosis" axis. VEGF family members are critical regulators of tissue repair but may also promote inflammation and scarring depending on receptor-specific activation. Over the past decade, evidence has highlighted VEGF's pivotal role in scar formation, with elevated levels linked to normal scars, hypertrophic scars, and keloids. Experimental studies demonstrate that VEGF inhibition reduces scar tissue deposition. Notably, VEGFR-2 activation accelerates skin healing, while VEGFR-1/VEGFR-3 activation may drive inflammation and fibrosis. Selective VEGFR-2 stimulation via viral VEGF-E enhances IL-10 expression, reduces macrophage infiltration and myofibroblast differentiation, improves microvascular density, and promotes pericyte coverage in healed wounds. Epidermal growth factor (EGF), another key peptide, coordinates cell growth, proliferation, and differentiation during healing. Recombinant human EGF (rhEGF) is widely used to accelerate repair by stimulating epithelialization, shortening the inflammatory phase, and promoting organized collagen remodeling, thereby reducing fibrosis [21].

3. Inflammatory Factors and Hyperplasia of Fibroblasts

3.1. Activation and Proliferation of Fibroblasts

The primary characteristics of skin scar formation include persistent activation of myofibroblasts and excessive extracellular matrix (ECM) deposition. The exact mechanisms underlying scar formation remain unclear. However, fibroblasts are considered key cells involved in scar formation, as their abnormal proliferation and excessive collagen deposition often lead to scarring. ECM remodeling is mediated by myofibroblasts, which are differentiated fibroblasts [22]. Studies indicate that myofibroblasts exhibit robust ECM-secreting capabilities and represent an activated form of resident wound tissue fibroblasts. As the most critical effector cells associated with scar formation, myofibroblasts are typically activated during inflammatory responses.

3.2. Regulatory Roles of Cytokines

Cytokines such as IGF-1, HIF-1, PDGF, and TGF-β play vital regulatory roles in fibroblast proliferation and differentiation. They influence the synthesis and degradation of the extracellular matrix by modulating fibroblast signaling pathways and gene expression. During pathological scar formation, hyperdifferentiated myofibroblasts exhibit uncontrolled ECM production, secrete cytokines, and become hypersensitive even to low concentrations of growth factors. Overdifferentiated

keratinocytes produce fibrotic factors, including vascular endothelial growth factor, epidermal growth factor, connective tissue growth factor, insulin-like growth factor 1, and excessive TGF-β, which promote fibrosis through fibroblast hyperproliferation and collagen overproduction at wound sites. Dysregulation of TGF-β superfamily members, such as activin, also contributes to chronic wound healing and excessive scarring. Activin promotes wound healing by stimulating granulation tissue formation and keratinocyte proliferation [22]. Cytokine networks and signaling pathways exhibit cross-regulation: for example, TGF-β1 induces IL-6 expression, while IL-6 enhances TGF-β receptor stability via STAT3, forming a positive feedback loop. Combined local delivery of TGF-β inhibitors and IL-10 synergistically inhibits fibrosis and promotes tissue remodeling. Additionally, IL-10 significantly suppresses keloid fibroblast proliferation and differentiation by inhibiting the TGF-β/Smad signaling pathway, consistent with findings from previous studies by Shi *et al.* [23].

4. Relationship between Oxidative Stress and Inflammatory Factors

4.1. Concept and Impact of Oxidative Stress

Oxidative stress arises from the generation of oxygen- and nitrogen-based free radicals and the imbalance in cellular antioxidant mechanisms. This state is driven and mediated by free radicals released through physiological aerobic metabolic pathways and pathological inflammatory responses. Free radicals include reactive oxygen species (ROS) and reactive nitrogen species (RNS), with ROS encompassing superoxide anions (O_2^-), peroxides, hydroxyl radicals (HO·), and singlet oxygen ($^1O_2$) [24]. In the body, when ROS production exceeds normal levels or antioxidant defense mechanisms weaken, significant accumulation of ROS and its derivatives occurs. This state poses toxic threats to cellular structures and tissue functions, constituting a pathological condition. NAD^+ and NADH act as coenzymes, providing redox capacity for mitochondrial ATP generation. NAD^+ serves as the precursor for NADP and NADPH, which protect cells from ROS damage. Conversely, NADPH oxidase 2 (NOX2) catalyzes molecular oxygen to generate superoxide, a major source of cellular ROS. Excessive ROS production leads to intracellular oxidative stress and inflammation [25].

4.2. Pro-Inflammatory Mechanism of Oxidative Stress

In keloid tissues, the TGF-β1/SMAD signaling pathway is significantly activated, accelerating the progression of dermal fibrosis. Elevated ROS levels have been observed in keloid fibroblasts. Specifically, TGF-β1 enhances the fibrotic characteristics of fibroblasts and promotes the expression of early growth response factor 1 (EGR1) through precise regulation of the SMAD signaling pathway in keloids. EGR1 plays a critical role by directly targeting NADPH oxidase 4 (NOX4), effectively regulating ROS generation. Furthermore, NOX4-derived ROS promotes the fibrotic-like phenotype of keloid fibroblasts and plays a key role in keloid fibrosis

[26]. Under oxidative stress, miR-21 (pro-fibrotic) is upregulated, while miR-29 (anti-fibrotic) is downregulated, exacerbating extracellular matrix (ECM) deposition. ROS also activates multiple signaling pathways: for example, ROS triggers ERK, JNK, and p38 MAPK pathways to induce fibroblast proliferation, while simultaneously upregulating pro-inflammatory factors (IL-6, TNF-α) via NF-κB, forming an inflammation-fibrosis positive feedback loop. This process induces the expression and release of inflammatory factors. Concurrently, inflammatory factors further promote ROS production and accumulation, creating a vicious cycle. Such interactions exacerbate scar formation and progression.

5. Role of MicroRNA in Regulating Inflammatory Factors

5.1. Overview of MicroRNA

MicroRNAs (miRNAs) are small, endogenous, non-coding single-stranded RNA molecules composed of 18 - 22 nucleotides (nt). They post-transcriptionally regulate gene expression by directly binding to the 3' untranslated region (UTR) of target mRNAs [27]. Numerous types of non-coding RNAs have been identified, which are abundant and capable of modulating gene expression. These include transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), small RNAs such as microRNAs (miRNAs) and small interfering RNAs (siRNAs), as well as long non-coding RNAs (lncRNAs). Recent studies have revealed distinct expression levels of miRNAs and lncRNAs in keloid tissues and keloid-derived fibroblasts compared to normal tissues and fibroblasts, suggesting that non-coding RNAs may play a role in the pathogenesis of keloids [28].

5.2. miRNA Regulation of Inflammatory Factors

In recent years, research on miRNAs has grown significantly, spanning fields from tissue repair to targeted cancer therapies. This study demonstrates that miR-152-5p expression is markedly reduced in keloid tissues and their constituent cells. Through regulatory mechanisms, this miRNA inhibits Smad3 expression in keloids, thereby suppressing cell proliferation and migration while promoting apoptosis. MiR-152-5p may exert anti-fibrotic effects in keloids by modulating Smad3-mediated activation of Erk1/2 and Akt [29]. Similarly, miR-182-5p inhibits fibrosis and scar formation in hypertrophic fibroblasts (HFs) via the SMAD4 pathway, with its anti-scarring effects potentially linked to the regulation of proliferation, apoptosis, and migration [30]. Overexpression of miR-149 in HaCaT cells downregulates the expression of pro-inflammatory cytokines IL-1α, IL-1β, and IL-6 under both basal and inflammatory conditions. Furthermore, miR-149 indirectly enhances the expression of transforming growth factor-β3 (TGF-β3) and type III collagen in fibroblasts, which are essential for extracellular matrix remodeling [31]. TGF-β1, which is upregulated in keloid tissues, promotes the proliferation, collagen production, and differentiation of dermal fibroblasts. During keloid formation, the interaction between TGF-β1 and miR-21 plays a central role in regulating FasL protein. Concurrently, activation of the PTEN/AKT signaling path-

way and upregulation of miR-21 collectively contribute to TGF-β1-mediated proliferation and transdifferentiation of keloid fibroblasts (KFs). Inhibition of miR-21 expression effectively reduces KF proliferation and impedes transdifferentiation, suggesting that miR-21 may serve as a therapeutic target for keloids. Additionally, another study found that miR-21 promotes collagen production in keloids by negatively regulating Smad7 [32]. These findings provide novel insights into the potential application of miRNAs in the prevention and treatment of pathological scarring.

6. Summary and Conclusion

In summary, oxidative stress, microRNAs, inflammatory factors, cytokines, and growth factors play crucial roles in the formation and development of pathological scars. Their complex interactions promote fibroblast proliferation and differentiation, induce extracellular matrix synthesis, and regulate immune responses through multiple mechanisms, collectively contributing to scar formation. Therefore, in-depth investigation of the relationship between inflammatory factors and pathological scars, along with exploration of the underlying molecular mechanisms, holds significant importance for developing effective prevention and treatment approaches. Future research should focus on elucidating specific signaling pathways and regulatory networks of inflammatory factors, thereby providing novel therapeutic targets and strategies for managing pathological scars.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Wang, Z., Zhao, W., Cao, Y., Liu, Y., Sun, Q., Shi, P., *et al.* (2020) The Roles of Inflammation in Keloid and Hypertrophic Scars. *Frontiers in Immunology*, **11**, Article 603187. https://doi.org/10.3389/fimmu.2020.603187

[2] Li, Y.L., Li, L.H., Zheng, Z.L., *et al.* (2022) Research Progress on Inflammatory Factors and Signaling Pathways in Keloid. *Chinese Journal of Dermatology and Venereology*, **36**, 479-483.

[3] Best, K.T., Nichols, A.E.C., Knapp, E., Hammert, W.C., Ketonis, C., Jonason, J.H., *et al.* (2020) NF-κB Activation Persists into the Remodeling Phase of Tendon Healing and Promotes Myofibroblast Survival. *Science Signaling*, **13**, Article No. 658. https://doi.org/10.1126/scisignal.abb7209

[4] Liu, Z.K., Rong, X.Z. and Li, Q.H. (2022) Efficacy of Scar Tissue Excision Combined with Medium-Thickness Skin Grafting in the Treatment of Deep Burns. *Chinese and Foreign Medical Research*, **20**, 1-4.

[5] Shao, Y., Guo, Z., Yang, Y., Liu, L., Huang, J., Chen, Y., *et al.* (2022) Neutrophil Extracellular Traps Contribute to Myofibroblast Differentiation and Scar Hyperplasia through the Toll-Like Receptor 9/Nuclear Factor Kappa-B/Interleukin-6 Pathway. *Burns & Trauma*, **10**, c44. https://doi.org/10.1093/burnst/tkac044

[6] Wang, L.Z., Liu, Z.G. and Zhang, Z.Q. (2024) BMSCs Inhibit Glial Inflammatory Response and Scar Formation via TLR4/NF-κB Signaling Pathway. *Chinese Journal of*

Gerontology, **44**, 2467-2471.

[7] Zhang, S., Xu, Y., Huang, M., Cao, X., Chen, X., Liu, Y., *et al.* (2018) Saikosaponin a Increases Interleukin-10 Expression and Inhibits Scar Formation after Sciatic Nerve Injury. *Neural Regeneration Research*, **13**, 1650-1656. https://doi.org/10.4103/1673-5374.237139

[8] Shi, J., Shi, S., Xie, W., Zhao, M., Li, Y., Zhang, J., *et al.* (2021) IL-10 Alleviates Lipopolysaccharide-Induced Skin Scarring via IL-10R/STAT3 Axis Regulating TLR4/NF-κB Pathway in Dermal Fibroblasts. *Journal of Cellular and Molecular Medicine*, **25**, 1554-1567. https://doi.org/10.1111/jcmm.16250

[9] Baron, J.M., Glatz, M. and Proksch, E. (2020) Optimal Support of Wound Healing: New Insights. *Dermatology*, **236**, 593-600. https://doi.org/10.1159/000505291

[10] Guillamat-Prats, R. (2021) The Role of MSC in Wound Healing, Scarring and Regeneration. *Cells*, **10**, Article No. 1729. https://doi.org/10.3390/cells10071729

[11] Zhang, M., Xu, Y., Liu, Y., Cheng, Y., Zhao, P., Liu, H., *et al.* (2016) Chemokine-Like Factor 1 (CKLF-1) Is Overexpressed in Keloid Patients. *Medicine*, **95**, e3082. https://doi.org/10.1097/md.0000000000003082

[12] Tan, J. and Wu, J. (2017) Current Progress in Understanding the Molecular Pathogenesis of Burn Scar Contracture. *Burns & Trauma*, **5**, Article No. 14. https://doi.org/10.1186/s41038-017-0080-1

[13] Wang, X., Wang, X., Liu, Z., Liu, L., Zhang, J., Jiang, D., *et al.* (2024) Identification of Inflammation-Related Biomarkers in Keloids. *Frontiers in Immunology*, **15**, Article 1351513. https://doi.org/10.3389/fimmu.2024.1351513

[14] Huang, Y., Xu, X.S., Chen, K., *et al.* (2022) Expression Levels of Progranulin and Cyclooxygenase-2 in Hypertrophic Scar Tissues after Burns and Their Correlation with Inflammatory Factors. *Guangxi Medical Journal*, **44**, 2709-2712.

[15] Ma, L., Hua, L., Yu, W., Ke, L. and Li, L. (2022) TSG-6 Inhibits Hypertrophic Scar Fibroblast Proliferation by Regulating IRE1α/TRAF2/NF-κB Signalling. *International Wound Journal*, **20**, 1008-1019. https://doi.org/10.1111/iwj.13950

[16] Moretti, L., Stalfort, J., Barker, T.H. and Abebayehu, D. (2022) The Interplay of Fibroblasts, the Extracellular Matrix, and Inflammation in Scar Formation. *Journal of Biological Chemistry*, **298**, Article ID: 101530. https://doi.org/10.1016/j.jbc.2021.101530

[17] Kidzeru, E.B., Lebeko, M., Sharma, J.R., Nkengazong, L., Adeola, H.A., Ndlovu, H., *et al.* (2023) Immune Cells and Associated Molecular Markers in Dermal Fibrosis with Focus on Raised Cutaneous Scars. *Experimental Dermatology*, **32**, 570-587. https://doi.org/10.1111/exd.14734

[18] Komi, D.E.A., Khomtchouk, K. and Santa Maria, P.L. (2019) A Review of the Contribution of Mast Cells in Wound Healing: Involved Molecular and Cellular Mechanisms. *Clinical Reviews in Allergy & Immunology*, **58**, 298-312. https://doi.org/10.1007/s12016-019-08729-w

[19] Čoma, M., Fröhlichová, L., Urban, L., Zajíček, R., Urban, T., Szabo, P., *et al.* (2021) Molecular Changes Underlying Hypertrophic Scarring Following Burns Involve Specific Deregulations at All Wound Healing Stages (Inflammation, Proliferation and Maturation). *International Journal of Molecular Sciences*, **22**, Article No. 897. https://doi.org/10.3390/ijms22020897

[20] Sorg, H., Tilkorn, D.J., Hager, S., Hauser, J. and Mirastschijski, U. (2016) Skin Wound Healing: An Update on the Current Knowledge and Concepts. *European Surgical Research*, **58**, 81-94. https://doi.org/10.1159/000454919

[21] Zhu, B., Tong, G., Gao, P. and Yan, M. (2024) Evaluating the Impact of Recombinant Human Epidermal Growth Factor on Scar Formation in Oral and Maxillofacial Traumatic Wound Healing. *International Wound Journal*, **21**, e14851. https://doi.org/10.1111/iwj.14851

[22] Xiaojie, W., Banda, J., Qi, H., Chang, A.K., Bwalya, C., Chao, L., *et al.* (2022) Scarless Wound Healing: Current Insights from the Perspectives of TGF-β, KGF-1, and KGF-2. *Cytokine & Growth Factor Reviews*, **66**, 26-37. https://doi.org/10.1016/j.cytogfr.2022.03.001

[23] Shi, C.K., Zhao, Y.P., Ge, P., *et al.* (2019) Therapeutic Effect of Interleukin-10 in Keloid Fibroblasts by Suppression of TGF-Beta/Smad Pathway. *European Review for Medical and Pharmacological Sciences*, **23**, 9085-9092.

[24] Li, Y., Gong, L., Chu, C., *et al.* (2023) Research Progress on Oxidative Stress in Pathological Scars. *Chinese Journal of Medical Aesthetics and Cosmetology*, **29**, 331-334.

[25] He, T., Bai, X., Li, Y., Zhang, D., Xu, Z., Yang, X., *et al.* (2023) Insufficient SIRT1 in Macrophages Promotes Oxidative Stress and Inflammation during Scarring. *Journal of Molecular Medicine*, **101**, 1397-1407. https://doi.org/10.1007/s00109-023-02364-x

[26] Qin, H., Zhang, L., Li, M., Liu, Y., Sun, S., Nie, W., *et al.* (2022) EGR1/NOX4 Pathway Regulates Oxidative Stress and Further Facilitates Fibrosis Progression in Keloids Responses to TGF-β1. *Journal of Dermatological Science*, **108**, 138-145. https://doi.org/10.1016/j.jdermsci.2022.12.009

[27] Liu, M., Zhao, D., Wu, X., Guo, S., Yan, L., Zhao, S., *et al.* (2019) Mir-466 and NUS1 Regulate the AKT/nuclear Factor Kappa B (NFκB) Signaling Pathway in Intrauterine Adhesions in a Rat Model. *Medical Science Monitor*, **25**, 4094-4103. https://doi.org/10.12659/msm.914202

[28] Tsai, C. and Ogawa, R. (2019) Keloid Research: Current Status and Future Directions. *Scars, Burns & Healing*, **5**, 1-8. https://doi.org/10.1177/2059513119868659

[29] Pang, Q., Wang, Y., Xu, M., Xu, J., Xu, S., Shen, Y., *et al.* (2019) MicroRNA-152-5p Inhibits Proliferation and Migration and Promotes Apoptosis by Regulating Expression of Smad3 in Human Keloid Fibroblasts. *BMB Reports*, **52**, 202-207. https://doi.org/10.5483/bmbrep.2019.52.3.278

[30] Jin, M. and Xu, X. (2023) MicroRNA-182-5p Inhibits Hypertrophic Scar Formation by Inhibiting the Proliferation and Migration of Fibroblasts via SMAD4 Pathway. *Clinical, Cosmetic and Investigational Dermatology*, **16**, 565-580. https://doi.org/10.2147/ccid.s397808

[31] Lang, H., Zhao, F., Zhang, T., Liu, X., Wang, Z., Wang, R., *et al.* (2017) MicroRNA-149 Contributes to Scarless Wound Healing by Attenuating Inflammatory Response. *Molecular Medicine Reports*, **16**, 2156-2162. https://doi.org/10.3892/mmr.2017.6796

[32] Lv, W., Ren, Y., Hou, K., Hu, W., Yi, Y., Xiong, M., *et al.* (2020) Epigenetic Modification Mechanisms Involved in Keloid: Current Status and Prospect. *Clinical Epigenetics*, **12**, Article No. 183. https://doi.org/10.1186/s13148-020-00981-8